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(54) Title: 5'-INDOLINYL OXAZOLIDINONES USEFUL AGAINST *MYCOBACTERIUM TUBERCULOSIS*

(57) Abstract

5-(S)-N-(1'-Hydroxyacetyl-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone and 5-(S)-N-(1'-(2-thiophenecarbonyl)-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone are useful in treating tuberculosis caused by *M. Tuberculosis.*

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5'-INDOLINYL OXAZOLIDINONES USEFUL AGAINST *MYCOBACTERIUM TUBERCULOSIS*

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention is the use of two 5'-indolinyl oxazolidionones (I) to treat tuberculosis (TB) caused by *M. tuberculosis*.

2. Description of the Related Art

Tuberculosis (TB) is a well known disease which is caused by *M. tuberculosis*.

At present various agents are used to treat those infected with TB. The most common of these pharmaceutical agents include isoniazid, rifampin, ethambutol, p-aminosalicylic acid, pyrazinamide, streptomycin, capreomycin, cycloserine, ethionamide and kanamycin and aminoglycosides antibiotics and mixtures thereof.

Since the introduction of antibiotics and the better health care practices in the 1950's, the incidence of TB had declined an average of six percent per year until 1985. Since then there has been a 16 percent per year increase in new TB cases. This increased incidence of TB has been accompanied by outbreaks of multi-drug resistant strains of *M. tuberculosis*. Because TB has never declined in incidence in the developing and underdeveloped countries and the additional cases related to the increase in AIDS, the World Health Organization recently established a Working Group to develop new antibiotics to treat TB which are urgently needed.

While there are pharmaceutical agents presently available to treat those infected with TB, it is highly desirable to have a better agent because of the development of *M. tuberculosis* strains resistant to current therapeutics.

US Patent 4,128,654 discloses 5-halomethylphenyl-2-oxazolidinones which are useful in controlling fungal and bacterial diseases of plants.

US Patent 4,250,318 discloses 3-substituted phenyl-5-hydroxymethyloxazolidinones having antidepressive utility.

US Reissue Patent 29,607 discloses 3-substituted phenyl-5-hydroxymethyloxazolidinones having antidepressive, tranquilizing and sedative utility.

US Patent 4,340,606 discloses 3-(p-alkylsulfonyl)phenyl-5-(hydroxymethyl or acyloxymethyl)oxazolidinones having antibacterial activity in mammals.

Belgium Patent 892,270 discloses 3-(arylalkyl, arylalkenyl or arylacetylenic substituted)phenyl)-5-(aminomethyl)oxazolidinones which are inhibitors of monoamine oxidase.

US Patent 4,461,773 discloses 3-substituted phenyl-5-hydroxymethyloxazolidinones which have antibacterial activity.

European Patent Publications 127,902 and 184,170 disclose 3-substituted phenyl-5-amidomethyloxazolidinones which have antibacterial utility.

Antimicrobial Agents and Chemotherapy 1791 (1987) discusses compounds disclosed in European Patent Publications 127,902 and 184,170, discussed above, and compares these new compounds with known antibiotics.

US Patent 4,705,799 discloses aminomethyloxooxazolidinyl benzene derivatives including sulfides, sulfoxides, sulfones and sulfonamides which possess antibacterial activity.

US Patent 4,801,600 discloses 6'-indolinyloxazolidinones (where the indolinyl nitrogen is meta to the oxazolidinone nitrogen).

US Patents 5,036,092 and 5,039,690 disclose 6'-indolinyl oxazolidinones whereas the compound of the present invention is a 5'-indolinyl oxazolidinone.

Diagn. Microbiol. Infect. Dis., 14, 465-471 (1991) discloses that an oxazolidinone, (+)-DUP-721 is active against tuberculosis.

5'-indolinyl oxazolidinones are known, see International Publication No. WO90/02744, published March 22, 1990 based on International Patent Application No. PCT/US89/03548 filed August 22, 1989. More particularly, 3-(5'-1-hydroxyacetylindolinyl)-5ß-(acetamidomethyl)-oxazolidin-2-one more preferably termed 5-(S)-N-(1'-hydroxyacetyl-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone is known, see International Publication No. WO90/02744, EXAMPLES 122. The optically active from of the compound is disclosed in EXAMPLE 150. 5-(S)-N-(1'-(2-Thiophenecarbonyl)-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone is also known, see EXAMPLE 146 of International Publication No. WO90/02744.

SUMMARY OF INVENTION

Disclosed is a method of treating humans who have tuberculosis caused by *Mycobacterium tuberculosis* which comprises admisitration of an effective amount of a 5'-indolinyl oxazolidinone selected from the group consisting of

5-(S)-N-(1'-hydroxyacetyl-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone and

5-(S)-N-(1'-(2-thiophenecarbonyl)-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone

and pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

5'-indolinyl oxazolidinones are known, see International Publication No. WO90/02744, the compounds of formula (XI). The 5'-indolinyl oxazolidinones contain an asymmetric center and therefore produce two enantiomers one "S" and the other "R", either of which can be (+/d) and the other (-/l). (+)-3-(5'-1-Hydroxyacetylindolinyl)-5ß-(acetamidomethyl)oxazolidin-2-one is known, see International Publication No. WO90/02744, EXAMPLES 122. The antibacterially active form of the compound is the "S" enantiomer and is disclosed in EXAMPLE 150 as obtained by resolution of a racemic mixture. The optically active form was termed 3-(5'-1-hydroxyacetylindolinyl)-5ß-(acetamidomethyl)oxazolidin-2-one in International Publication No. WO90/02744. However, a preferred name is 5-(S)-N-(1'-hydroxyacetyl-5'-indolinyl)-5-

(acetamidomethyl)-2-oxazolidinone. 5-(S)-N-(1'-(2-Thiophenecarbonyl)-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone is also known, see EXAMPLE 146 of International Publication No. WO90/02744.

While the racemic forms of the oxazolidinones are useful in treating TB, it is highly preferable to use the active enantiomer rather than the racemic form. While the optically active form can be obtained by resolution of a racemic mixture as set forth in International Publication No. WO90/02744, it is preferred to prepare the desired enantiomer by a stereoselective synthesis. One method to produce 5-(S)-N-(1'-hydroxyacetyl-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone is by resolution of the racemic form. Another method is by the process of EXAMPLES 1-9. The preferred method, as discussed below, is by the process of EXAMPLES 14-19. Likewise, one method to produce 5-(S)-N-(1'- -thiophenecarbonyl)-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone is by resolution of the racemic form. Another method is by the process of EXAMPLES 10-13. The preferred method, as discussed below, is by the process of EXAMPLES 14-17 and 20.

The preferred method of making the optically active is by starting with the known 1-carbo-t-butyloxy-(N-carbobenzyloxy)-5-aminoindoline [US Patent 5,164,510, EXAMPLE 11, compound (IV)] in a solution of tetrahydrofuran or ether at -78° under an inert atmosphere, preferrably nitrogen, and treating with n-butyl lithium/hexane, followed by the addition of (R)-glycidyl butyrate and allowing the mixture to warm to 20-25°. This method produces in high yield the optically active 5-hydroxymethyl oxazolidinone having the desired stereochemistry (R), i.e., the 5-β configuration, see EXAMPLE 14.

This alcohol is then treated with triphenylphosphine and diethylazodicarboxylate in tetrahydrofuran or ether, to give the optically active 5-phthalimidomethyl oxazolidinone, see EXAMPLE 15.

EXAMPLE 16 discloses that the 5-phthalimidomethyl compound is then treated with a reagent to remove the phthalimide group such as an aqueous solution of methylamine or hydrazine to give the intermediate 5-aminomethyl oxazolidinone. This is not purified, but is immediately acetylated by treatment with acetic anhydride or acetyl chloride in pyridine or methylene chloride to give the (S)-5-acetamidomethyl oxazolidinone with the [carbo-t-butyloxy]-protecting group on the indolinyl nitrogen.

EXAMPLE 17 discloses the removal of the protecting group by the addition of trifluoroacetic acid, either neat, or in methylene chloride, to give the parent indoline oxazolidinone.

EXAMPLE 18 discloses acylation on the indoline nitrogen is effected by the addition of benzyloxylacetyl chloride in the presence of triethylamine or diisopropylethylamine in methylene chloride or ether, to give the benzyloxyacetylindolinyl compound. Treatment of this compound

with hydrogen in the presence of palladium black or palladium/charcoal in ethyl acetate or methanol (EXAMPLE 19) gives (S)-5-acetamidomethyl 3(5'-1-hydroxyacetylindolinyl)-oxazolidinone.

When the product of EXAMPLE 17 is acylated with 2-thiophenecarbonyl chloride (EXAMPLE 20) the product is 5-(S)-N-(1'-(2-thiophenecarbonyl)-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone.

The 5'-indolinyl oxazolidinones are administered either parenterally or orally. It is known to those skilled in the art how to formulate the 5'-indolinyl oxazolidinones into appropriate pharmaceutical dosage forms for oral (tablet, capsule) or parenteral (sterile solution) use utilizing an appropriate solvent such as propylene glycol.

The 5'-indolinyl oxazolidinones are useful in treating tuberculosis in humans infected with strains of *M. tuberculosis* which are susceptible to these antibiotics. The 5'-indolinyl oxazolidinones are administered at doses from about 50 to about 3,000 mg/day. It is preferred that the 5'-indolinyl oxazolidinones are administered at doses of about 100 to about 2,000 mg/day. The 5'-indolinyl oxazolidinones are administered orally and the total daily dose is divided between one to four doses per day.

The 5'-indolinyl oxazolidinones can either be used alone, or used in combination with each other or with other antibiotics as is known to those skilled in the art. Preferred drugs to be used in combination with 5'-indolinyl oxazolidinones include, but are not limited to, isoniazid, rifampin, ethambutol, p-aminosalicylic acid, pyrazinamide, streptomycin, kanamycin, capreomycin, cycloserine, and ethionamide.

It is known to those skilled in the art how to determine if humans are infected with *M. tuberculosis*, and how to determine if these organisms are susceptible to the 5'-indolinyl oxazolidinones.

The exact dosage and frequency of administration depends on the particular 5'-indolinyl oxazolidinones used, the particular condition being treated, the severity of the condition being treated, the age, weight, general physical condition of the particular patient, other medication the individual may be taking as is well known to those skilled in the art and can be more accurately determined by measuring the blood level or concentration of the 5'-indolinyl oxazolidinones in the patient's blood and/or the patient's response to the particular condition being treated.

DEFINITIONS AND CONVENTIONS

The definitions and explanations below are for the terms as used throughout this entire document including both the specification and the claims.

DEFINITIONS

All temperatures are in degrees Centigrade.

TLC refers to thin-layer chromatograph.

THF refers to tetrahydrofuran.

Saline refers to an aqueous saturated sodium chloride solution.

When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

IR refers to infrared spectroscopy.

$[\alpha]_D^{25}$ refers to the angle of rotation of plant polarized light (specific optical rotation) at 25° with the sodium D line (5893A).

MS refers to mass spectrometry expressed as m/e or mass/charge unit. $[M + H]^+$ refers to the positive ion of a parent plus a hydrogen atom. EI refers to electron impact. CI refers to chemical ionization. FAB refers to fast atom bombardment.

Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

M. tuberculosis refers to *Mycobacterium tuberculosis*.

EXAMPLES

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

EXAMPLE 1 N-Benzyloxyacetyl-5-nitro-indoline (A)

Triethylamine (45 ml) is added to a solution of 5-nitroindoline (42.05 g) in tetrahydrofuran (250 ml) and the mixture cooled to O°, then a solution of benzyloxyacetyl chloride (48.6 g) in THF (50 ml) is added over 15 min, and the mixture stirred in the ice bath for an additional 1.25 hr, then allowed to warm to 20-25° over 3 hr. Aqueous workup yields a solid which is recrystallized from acetone/water to give the title compound, mp 137-139°.

EXAMPLE 2 N-Benzyloxyacetyl-5-amino-indoline (B)

To a mixture of N-benzyloxyacetyl-5-nitro-indoline (A, EXAMPLE 1, 12.26 g) in methanol/ethyl acetate (18/82, 1.1 l) under nitrogen is added palladium/charcoal (10%, 1.55 g) and the flask alternately evacuated and filled with hydrogen from a balloon (3 times), then the mixture is allowed to stir at 20-25° for 4 hr. The mixture is degassed and then filtered over diatomaceous earth, and the pad washed with ethyl acetate. The filtrate is concentrated to a

volume of about 200 ml and a crystalline solid is precipitated, which is collected to give the title compound, mp 105-106°.

EXAMPLE 3 N-Benzyloxyacetyl-5-[(2'-(R)-hydroxy-3'-butyrate)propylamino]indoline (C)

The following procedure is a modification of that described by M. Chini, P. Crotti, and F. Macchia, "Metal salts as new catalysts for mild and efficient aminolysis of oxiranes," Tetrahedron Letters, 31, 4661 (1990). The prior art process uses a full equivalent of zinc chloride, but since it was found that the reaction stops due to complex formation, and side reactions are more prevalent, 5 mole % of zinc chloride is used.

In a flame dried flask, zinc chloride (0.12 g) is dissolved in dry acetonitrile (10 ml), then (R-)glycidyl butyrate (3.0 ml) is added and the mixture stirred at 20-25°, while N-benzyloxyacetyl-5-amino-indoline (B, EXAMPLE 2, 4.94 g) in acetonitrile (65 ml) is slowly added. The mixture is refluxed for a total of 2 days, then poured into 200 ml of water and extracted with ethyl acetate (5 x 50 ml). The phases are separated and the organic layers dried with magnesium sulfate and concentrated under reduced pressure to give an oil residue. This is carried on into the following reaction without purification; TLC analysis indicated a spot at Rf= 0.16 on silica gel, acetone/methylene chloride (10/90), for the desired compound. An analytical sample is purified using this system and gave a sample for MS, calcd for $C_{24}H_{30}O_5N_2$ = 426.2155, found = 426.2153.

EXAMPLE 4 5-(R)-N-(1'-benzyloxyacetyl-5'-indolinyl)-5-(butyryloxymethyl)-2-oxazolidinone (D)

To a mixture of N-benzyloxyacetyl-5-[(2'-(R)-hydroxy-3'-butyrate)propylamino]indoline (C, EXAMPLE 3, 5.8 g) in methylene chloride (255 ml) under nitrogen at -15° is added a solution of phosgene in toluene (1.93 M, 8.4 ml), and the mixture is allowed to slowly warm to 0° over 1 hr. After an additional 15 min, diisopropylethylamine (5.7 ml) is added in dropwise fashion over 5 min, and the mixture stirred in the ice bath for 50 min, then allowed to warm to 22°, then poured into 1 N hydrochloric acid (50 ml). The layers are separated and the aqueous is extracted with methylene chloride (3 x 25 ml). The combined organic layers are washed successively with (75 ml ea) saturated aqueous sodium bicarbonate, water, and saline, then dried magnesium sulfate, and concentrated under reduced pressure. The residue is purified on silica gel (6 cm x 38 cm column, 40-63 μ) with a gradient elution in acetone (2%-9%) in methylene chloride. The appropriate fractions are pooled and concentrated to give the title compound.

EXAMPLE 5 5-(R)-N-(1'-benzyloxyacetyl-5'-indolinyl)-5-(butyryloxymethyl)-2-oxazolidinone (D)

A mixture of N-benzyloxyacetyl-5-[(2'-(R)-hydroxy-3'-butyrate)propylamino]indoline

(C, EXAMPLE 3, 0.69 g) and carbonyldiimidazole (0.26 g) in THF (3 ml) is refluxed for 7 days, then an additional carbonyldiimidazole (0.26 g) and THF (0.5 ml) are added, and the mixture refluxed for 5 hr. The mixture is poured into 0.5 N aqueous hydrochloric acid, the layers separated, and the aqueous extracted with ethyl acetate, and purification as above gives the title compound, MS Calcd for $C_{25}H_{28}O_6N_2$ = 452.1947, found = 452.1940; IR (neat) 1742, 1668 cm^{-1}.

EXAMPLE 6 5-(R)-N-(1'-benzyloxyacetyl-5'-indolinyl)-5-(hydroxymethyl)-2-oxazolidinone (E)

To a solution of 5-(R)-N-(1'-benzyloxyacetyl-5'-indolinyl)-5-(butyryloxymethyl)-2-oxazolidinone (D, EXAMPLE 5, 0.050 g) in methanol (1 ml) is added sodium methoxide in methanol (25%, 2.5 µl), and the mixture is stirred at 20° for 1 hr, then the mixture is concentrated to give a residue. Purification on a 250 µ silica gel plate in ethyl acetate (3 elutions) gives the title compound, TLC R_f = 0.28 (ethyl acetate); FAB MS Calcd for $C_{21}H_{22}N_2O_5$ = 382.1529, found = 382.1529.

EXAMPLE 7 5-(R)-N-(1'-benzyloxyacetyl-5'-indolinyl)-5-(azidomethyl)-2-oxazolidinone (F)

Following the general procedure of US Patent 4,801,600 and making non-critical variations, 5-(R)-N-(1'-benzyloxyacetyl-5'-indolinyl)-5-(hydroxymethyl)-2-oxazolidinone (E, EXAMPLE 6) is converted to the azide by treatment with methanesulfonyl chloride and triethylamine in methylene chloride, followed by displacement with sodium azide in refluxing acetone-water. This is immediately carried into the following reaction.

EXAMPLE 8 5-(S)-N-(1'-benzyloxyacetyl-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone (H)

Following the general procedure of EXAMPLE 2 and making non-critical variations but taking care to monitor the reduction of the azide so that unwanted cleavage of the benzyl group does not take place, 5-(R)-N-(1'-benzyloxyacetyl-5'-indolinyl)-5-(azidomethyl)-2-oxazolidinone (F, EXAMPLE 7), is converted into an amine (G) by treatment with palladium/charcoal in 1 atm of hydrogen in ethyl acetate. Removal of the hydrogen gas and purging with nitrogen is followed by the addition of pyridine and acetic anhydride (2 mole equiv. each), and the reaction stirred at 20-25° for 12 hr, then filtered over diatomaceous earth, and the filtrate concentrated. The residue is purified by column chromatography using a gradient of methanol/ethyl acetate to give the title compound.

EXAMPLE 9 5-(S)-N-(1'-Hydroxyacetyl-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone (I)

5-(S)-N-(1'-benzyloxyacetyl-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone (H, EXAMPLE 8) is dissolved in ethyl acetate and the mixture purged with nitrogen gas, then

palladium/charcoal is added followed by hydrogen (balloon) and the mixture is stirred until TLC analysis shows complete conversion of the starting material. The mixture is filtered over diatomaceous earth, concentrated and the residue is purified by column chromatography on silical gel (methanol/ethyl acetate) to give the title compound.

EXAMPLE 10 N-(t-Butyloxycarbonyl)-5-[(2'-(R)-hydroxy-3'-butyrate)propylamino]-indoline (J)

Following the general procedure of EXAMPLE 3 and making non-critical variations but starting with N-(t-butyloxycarbonyl)-5-aminoindoline, the title compound is obtained.

EXAMPLE 11 5-(S)-N-(1'-(t-Butyloxycarbonyl)-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone (K)

Following the general procedure of EXAMPLES 4-8 and making non-critical variations but starting with N-(t-butyloxycarbonyl)-5-[(2'-(R)-hydroxy-3'-butyrate)propylamino]indoline (EXAMPLE 10), the title compound is obtained.

EXAMPLE 12 5(S)-N-(5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone (L)

A 20-fold excess of trifluoroacetic acid is added slowly over a period of about 5 min to 5-(S)-N-(1'-(t-butyloxycarbonyl)-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone (K, EXAMPLE 11) in methylene chloride at 0°. The mixture is stirred for 3 hr at that temperature. Then the mixture is neutralized by the slow addition of saturated aqueous sodium bicarbonate, the layers separated, and the aqeous phase is extracted with methylene chloride to give the title compound.

EXAMPLE 13 5-(S)-N-(1'-(2-Thiophenecarbonyl)-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone (P)

Following the general procedure of International Publication No. WO90/02744, EXAMPLE 18, and making non-critical variations and starting with 5(S)-N-(5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone (L, EXAMPLE 12) and using the appropriate corresponding acylating agent the title compound is obtained.

EXAMPLE 14 (R)-3-(5'-1-Carbo-t-butyloxyindolinyl)-5-(hydroxymethyl)-oxazolidin-2-one

n-Butyl lithium/hexane (1.6 M, 16.7 ml) is added dropwise over 5 min to a mixture of 1-carbo-t-butyloxy-(N-carbobenzyloxy)-5-aminoindoline (IV, US Patent 5,164,510, EXAMPLE 11, 9.371 g) in freshly distilled tetrahydrofuran (140 ml) at -78° under nitrogen. The mixture is stirred for 10 min, then (R)-glycidyl butyrate (4.0 ml) is added via syringe, the mixture is stirred for 1 hr at -78°, then slowly allowed to warm to 20° overnight.

Saturated aqueous ammonium chloride (100 ml) and water (200 ml) is added to the mixture and this mixture is extracted with ethyl acetate (125 ml, then 3 x 100 ml), and the combined organic layers are washed with saline, and dried over magnesium sulfate. The mixture is filtere and the

filtrate is concentrated to give a solid which is recrystallized from hot ethyl acetate/hexanes to give the title compound, mp 154-157°; $[\alpha]_D$=-40° ($CHCl_3$).

EXAMPLE 15 (R)-3-(5'-1-Carbo-t-butyloxyindolinyl)-5-(phthalimidomethyl)-oxazolidin-2-one

Diethylazodicarboxylate (3.45 mL) is added over 3 min to a mixture of (R)-3-(5'-1-carbo-t-butyloxyindolinyl)-5-(hydroxymethyl)-oxazolidin-2-one (EXAMPLE 14, 7.103 g), phthalimide (3.228 g) and triphenylphosphine (5.804 g) in freshly distilled tetrahydrofuran (175 ml) at 0o under nitrogen. The mixture is stirred at 0° for 45 min, then allowed to come to 20° overnight, and the volatile components removed on a rotary evaporator. The residue is purified by chromatography on silica gel 40-63 microns, 4.5 cm (height) x 10.0 cm (diameter) column, eluting with methylene chloride. The appropriate fractions are pooled and concentrated to give the title compound, $[\alpha]_D$ = -52° (CH_3CN); MS (EI, relative abundance) 463 (M^+, 7.5).

EXAMPLE 16 (S)-3-(5'-1-Carbo-t-butyloxyindolinyl)-5-(acetamidomethyl)-oxazolidin-2-one (K)

A mixture of (R)-3-(5'-1-carbo-t-butyloxyindolinyl)-5-(phthalimidomethyl)-oxazolidin-2-one (EXAMPLE 15, 8.826 g) in absolute ethanol (100 ml) and aqueous methylamine (40%, 50 ml) is heated to reflux under nitrogen for 1.5 hr. The volatiles are then removed by reduced pressure with heat at 0.1 Torr to give a concentrate. To this concentrate is added 50 ml of pyridine and 25 ml of acetic anhydride at 20°. A slight exotherm occurred, so the flask is cooled in a water bath to maintain the temperature at about 30°. After stirring for 1.3 hr, the volatiles were removed by vacuum distillation (0.1 Torr), giving a residue. This residue is chromatographed on silica gel 40-63 micron, 9.6 cm dia x 4 cm height, eluting with a gradient of acetone in methylene chloride (0-50%, v/v). The appropriat fractions are pooled and concentrated to give a the title compound, mp = 153.5-155°.

EXAMPLE 17 (S)-3-(5'-indolinyl)-5-(acetamidomethyl)-oxazolidin-2-one (L)

Trifluoroacetic acid (5 ml) is added to a mixture of (S)-3-(5'-1-carbo-t-butyloxyindolinyl)-5-(acetamidomethyl)-oxazolidin-2-one (K, EXAMPLE 16, 4.705 g) in methylene chloride (40 ml) at 0° under nitrogen and the ice bath removed. After 4 hour, the mixture is concentrated and methylene chloride (8 ml) and trifluoroacetic acid (7 ml) is added at 20-25°. After stirring for an additional 2 hr, the mixture is concentrated under reduced pressure, and the residue is poured into saturated aqueous sodium bicarbonate and ice, and the mixture is continuously extracted with methylene chloride (500 ml) for 24 hr. The organic phases are combined, dried over magnesium sulfate and concentrated to give the title compound, mp 47-50°; TLC R_f = 0.11, methanol/ethyl acetate (10/90).

EXAMPLE 18 (S)-3-(5'-1-Benzyloxyacetylindolinyl)-5-(acetamidomethyl)-oxazolidin-2-one

Benzyloxyacetyl chloride (2.27 ml) is added dropwise over 5 min to a mixture of (S)-3-(5'-indolinyl)-5-(acetamidomethyl)-oxazolidin-2-one (L, EXAMPLE 17, 3.445 g) and triethylamine (2.62 ml) in methylene chloride (100 ml) at 0° under nitrogen. The mixture is slowly allowed to come to 20° overnight. The mixture is cooled to 0°, and filtered, the collected material is washed with water (2 x 50 ml) and dried in a vacuum oven at 70°. The solid is recrystallized from hot methylene chloride and hexanes to give the title compound, mp 188-189°, $[\alpha]_D$ = -13° ($CHCl_3$).

EXAMPLE 19 (S)-3-(5'-1-Hydroxyacetylindolinyl)-5-(acetamidomethyl)-oxazolidin-2-one (I)

A reaction flask holding a mixture of (S)-3-(5'-1-benzyloxyacetylindolinyl)-5-(acetamidomethyl)-oxazolidin-2-one (EXAMPLE 18, 9.119 g) in methanol/methylene chloride (10/90, 500 ml) is evacuated and filled with nitrogen gas three times, then 0.96 g of palladium black is added, and the flask again evacuated and filled with nitrogen three times, then evacuated and filled with hydrogen from a balloon (three times). After stirring of the mixture at 20-25° for a total of 4 hr, the hydrogen is removed and the mixture is filtered over diatomaceous earth, and the filtrate was concentrated in vacuo to give a solid. This solid is triturated with methanol/ethyl acetate (10/90, 200 ml) in a 35° bath, then cooled to 20°C and the solid collected to give the title compound, mp 198-199°, $[\alpha]_D$ = -21$_o$ (DMSO).

EXAMPLE 20 (S)-3-(5'-1-((2-Thiophenecarbonyl)indolinyl)-5-(acetamidomethyl)-oxazolidin-2-one (P)

Triethylamine (2.5 ml) followed by 2-thiophenecarbonyl chloride (1.5 ml) is added over 3 min to a mixture of (S)-3-(5'-indolinyl)-5-(acetamidomethyl)-oxazolidin-2-one (L, EXAMPLE 17, 3.289 g) in methylene chloride (70 ml) under nitrogen at 0°. The mixture is allowed to come to 20-25° overnight. The mixture is filtered, and the solid is washed with methylene chloride, followed by water, and then dried in a vacuum oven at 60°. The solid is recrystallized from acetone-water to give the title compound, mp = 193-198°, $[\alpha]_D$ = -38° (dimethylformamide).

EXAMPLE A 58 Year Old, 80 kg Male Infected With *M. tuberculosis*

A 58 yr old, 80 kg white male seeks medical attention due to an illness characterized by cough, weakness, night sweats and shortness of breath. The patient's chest radiograph shows extensive cavitary disease consistent with a diagnosis of tuberculosis. Sputum cultures are positive for *M. tuberculosis*, and the organism is found to be resistant to isoniazid, rifampin, and streptomycin. The patient is admitted to the hospital and given 5(S)-N-(1'-hydroxyacetyl-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone orally at a total dosage of 2000 mg/day for 4 weeks. Signs and symptoms of tuberculosis slowly disappear, viable *M. tuberculosis* organisms are no longer isolated from the patients sputum, and the patients chest radiograph returns to

normal. The patient is discharged from the hospital.

EXAMPLE B 30 Year Old, 60 Kg Female Infected With *M. tuberculosis*

A 30 yr old, 60 kg black female is diagnosed with pulmonary tuberculosis. Her sputum isolate is determined to be susceptible to both isoniazid and p-aminosalicylic acid. She is treated as an outpatient with a regimen of oral isoniazid and p-aminosalicylic acid, however, returns in 3 weeks because her condition does not improve. A new sputum culture grows *M. tuberculosis* that is resistant to isoniazid. The patient is given a 5(S)-N-(1'-hydroxyacetyl-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone to take orally at a dose of 1000 mg/day for two months, in addition to the other antibiotics. Within one month the signs and symptoms of tuberculosis slowly disappear. Sputum cultures taken 3, 6 and 12 months post-therapy are negative for *M. tuberculosis.*

EXAMPLE C 36 Year Old Male With AIDS Infected With *M. tuberculosis*

A 36 yr old white male with acquired immune deficiency syndrome (AIDS) presents to his physician with fever, weight loss, and cough. The chest radiograph reveals a focal nidus of infection in the lung. Expectorated sputum is negative for *M. tuberculosis*, however, a tissue biopsy taken via bronchoscopy contains culturable *M. tuberculosis.* In spite of a susceptibility report indicating the isolate is susceptible to the common therapy of isoniazid and rifampin, the patient is placed upon three drug therapy (isoniazid, rifampin, and ethambutol) due to his AIDS condition. The patient initially improves, but then his condition begins to relapse. A new sputum culture indicates the presence of *M. tuberculosis* that has developed resistance to rifampin, but is susceptible to 5(S)-N-(1'-hydroxyacetyl-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone. The rifampin portion of the regimen is replaced by 5-(S)-N-(1'-hydroxyacetyl-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone given at an oral dose of 1000 mg/day. Within 3 weeks the signs and symptoms of tuberculosis are resolved; the patient continues to take the three drug regimen for an additional 8 months. A sputum culture taken post-therapy is negative for *M. tuberculosis.* The patient is then given isoniazid prophylactically for life to prevent recurrence of the infection.

CLAIMS

1. Use of a 5'-indolinyl oxazolidinone selected from the group consisting of
5-(S)-N-(1'-hydroxyacetyl-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone and
5-(S)-N-(1'-(2-thiophenecarbonyl)-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone
and pharmaceutically acceptable salts thereof to prepare a medicament to treat humans who have tuberculosis caused by *Mycobacterium tuberculosis*.

2. Use according to claim 1 where the 5'-indolinyl oxazolidinone (I) is given orally.

3. Use according to claim 1 where the 5'-indolinyl oxazolidinone is
5-(S)-N-(1'-hydroxyacetyl-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone.

4. Use according to claim 1 where the 5'-indolinyl oxazolidinone is
5-(S)-N-(1'-(2-thiophenecarbonyl)-5'-indolinyl)-5-(acetamidomethyl)-2-oxazolidinone.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 93/04850

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/42

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X,Y	WO,A,9 002 744 (THE UPJOHN COMPANY) 22 March 1990 cited in the application see page 23, line 11 - line 15 see page 61; example 122 see page 66; examples 146,150	1-4
Y	DIAGN. MICROBIOL. INFECT. DIS. vol. 14, no. 6, 1991, pages 465 - 471 D.R. ASHTEKAR 'Oxazolidinones, a new class of synthetic antituberculosis agents.' cited in the application see the whole document	1-4

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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
10 SEPTEMBER 1993	22.09.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	ORVIZ DIAZ P.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	GOODMAN GILMAN, A. ET AL. (EDS.), 'GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS', 7TH EDITION, 1985, MACMILLAN PUBLISHING COMPANY, NEW YORK. see page 1210 - page 1211	1-4

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9304850
SA 74725

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 10/09/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		AU-A-	4195789	02-04-90
		EP-A-	0359418	21-03-90
		EP-A-	0434714	03-07-91
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		US-A-	5182403	26-01-93
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		JP-T-	4500665	06-02-92